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A RAPID ROUTE TO ERGOT PRECURSORS VIA AZA-CLAISEN REARRANGEMENT

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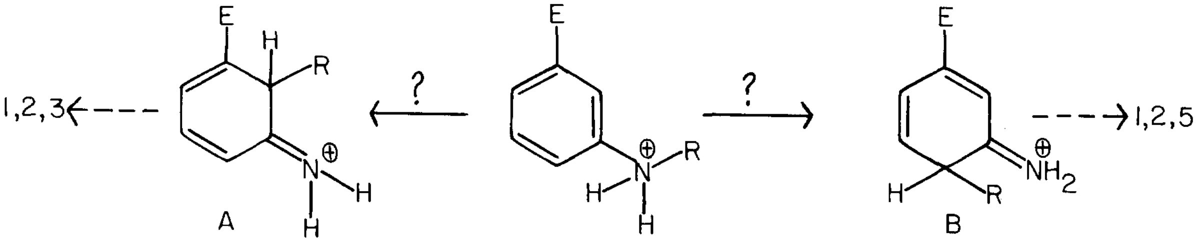
Summary: A new route to 4-substituted indoles involves aza Claisen rearrangement of a meta-substituted N-allyl aniline followed by ozonolytic cleavage of the resultant 1,2,3-trisubstituted aniline derivative.

The thermolytic Claisen rearrangement of phenyl allyl ethers to o-allylphenols has been widely used in the synthesis of various aromatic targets, including oxygen heterocycles.[1] By contrast, the corresponding rearrangement of N-allylanilines has not had a major impact in preparative chemistry.[2] The severe conditions required in the aza series are often accompanied by low yields.

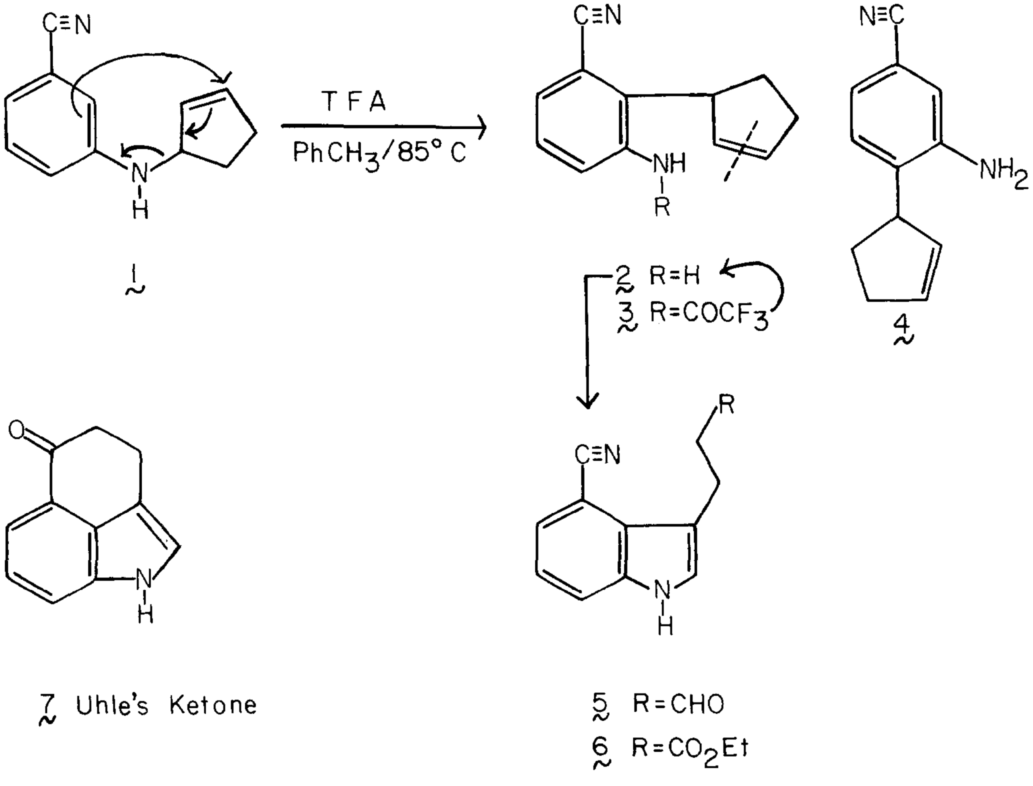
In some instances, Lewis Acid catalysis has been helpful in promoting the rearrangement of various allyl derivatives of aniline.[3] Recent reports from Russian laboratories described the rearrangement of protic acid salts of N-allylanilines under relatively mild conditions.[4a,b] In particular, trifluoroacetic acid salts were reported to rearrange with unusual facility.[4c]

Left unaddressed in this field, has been the question of regioselectivity in the rearrangement of meta-substituted anilinium salts. It seemed possible that with a strongly electron-withdrawing meta substituent of modest steric demands, the activation energy required to produce intermediate (A) might be lower than that required to reach intermediate (B), *wherein both electron-withdrawing groups are bound to the same double bond.*[5] An appealingly direct route to various ergoline structures, based on the analogies and conjectures advanced above, presented itself. Preliminary results are provided herein.

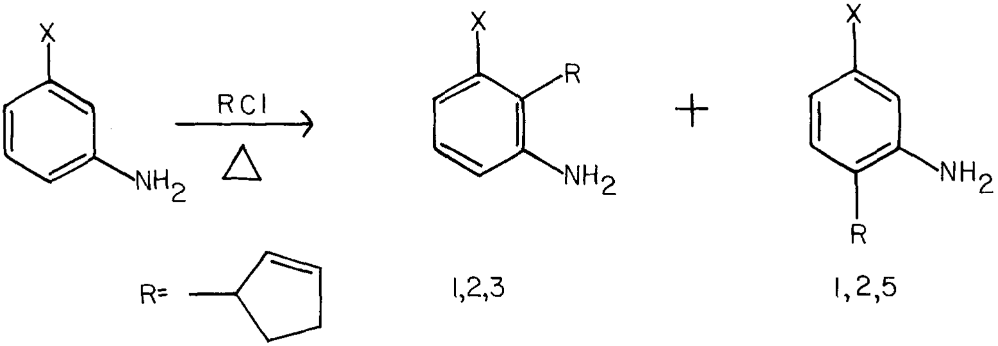


Reaction of m-cyanoaniline with 3-chlorocyclopentene (CH_2Cl_2; rt, 3.5/1, amine: chloride) afforded the alkylated product, 1. In a separate experiment, compound 1 was separated from starting materials and fully characterized. However, for the application at hand, the crude reaction mixture, containing compound 1 and excess starting material, was heated with 1.5 equiv. of trifluoroacetic acid in toluene at 85° for 12 h. Under these conditions, some of the resultant rearrangement product is converted to its trifluoroacetamide derivative 3. Accordingly, the total reaction mixture was reduced with sodium borohydride in ethanol. After chromatographic purification there was obtained a 38% yield of 2 (mp. of analytical sample = 82-83°). The isomeric compound was obtained in 10% yield.

Ozonlysis of 2, (CH_2Cl_2; -78°) followed by workup with dimethyl sulfide (rt, 12 h) afforded a 66% yield of the somewhat unstable aldehyde 5. Oxidation of crude 5 with Ag_2O in aqueous methanol followed by esterification with ethanolic HCl gave compound 6 (mp. 149-151°, lit[6] 153-154°) in 36% overall yield from 2. This compound had previously been converted to the key ergot intermediate, Uhle's ketone, (7).[6,7]



The isolated yields of homogeneous compounds **2** and **4** must be regarded as a minimum estimate of the quality of the rearrangement, owing to difficulties associated with processing of the trifluoroacetyl by-products. However, the ratio of the two rearrangement modes seems to be accurately represented by the ratio of the isolated yields. In earlier work, when the rearrangement was carried out on the hydrochloride salts of **1**,[4a] the ratio of **2**:**4** was somewhat less favorable (2.9:1). In the hydrochloride salt series the ratios of 1,2,3:1,2,5 products with several meta substituents were surveyed. The results are given below. Clearly, the cyano group was optimal for the objective at hand.



	X	Ratio (1,2,3:1,2,5)
(a)	C≡N	2.9:1
(b)	CO_2Me	1,2,3 product not observed
(c)	NO_2	1:10
(d)	F	1:3.7
(e)	CF_3	1:2

Further investigations into the aromatic aza-Claisen rearrangement are planned.

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